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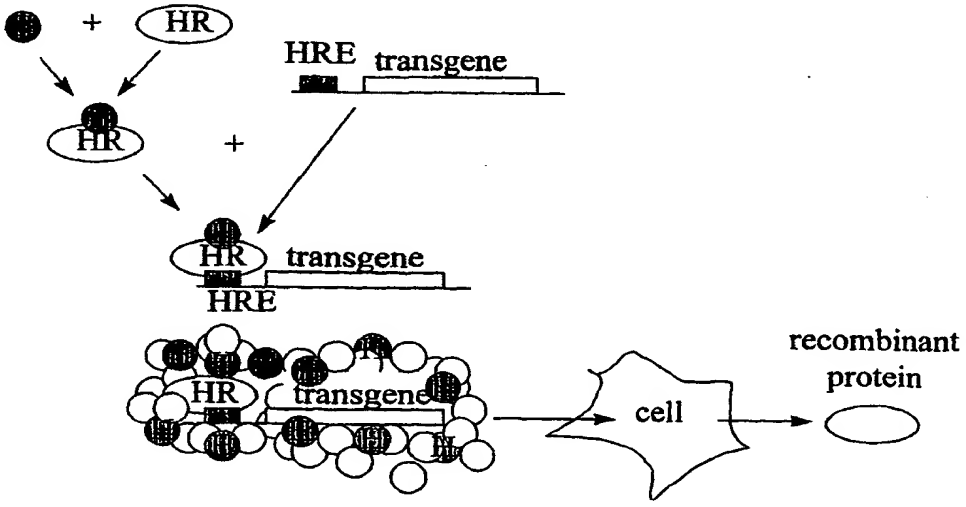
(54) Title: HORMONE–HORMONE RECEPTOR COMPLEXES AND NUCLEIC ACID CONSTRUCTS AND THEIR USE IN GENE THERAPY



(57) Abstract

The invention relates to the use of a nucleic acid contruct comprising at least one hormone responsive element and a transgene for preparing an agent for gene transfer. It further relates to particular nucleic acid contructs comprising at least one hormone responsive element and a transgene, wherein one of said at least one hormone responsive elements is not functionally linked to the transgene, vectors comprising such nucleic acid contructs and compositions of matter comprising such nucleic acid constructs wherein the hormone responsive elements of the constructs are coupled to a hormone–hormone receptor complex. The nucleic acid constructs, plasmids, and compositions of matter of the invention have applications in gene therapy, particularly in the treatment of human blood clotting disorders, such as hemophilia. They may also be used to up– or down–regulate target genes and for the delivery of vaccines.

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Fig. 1

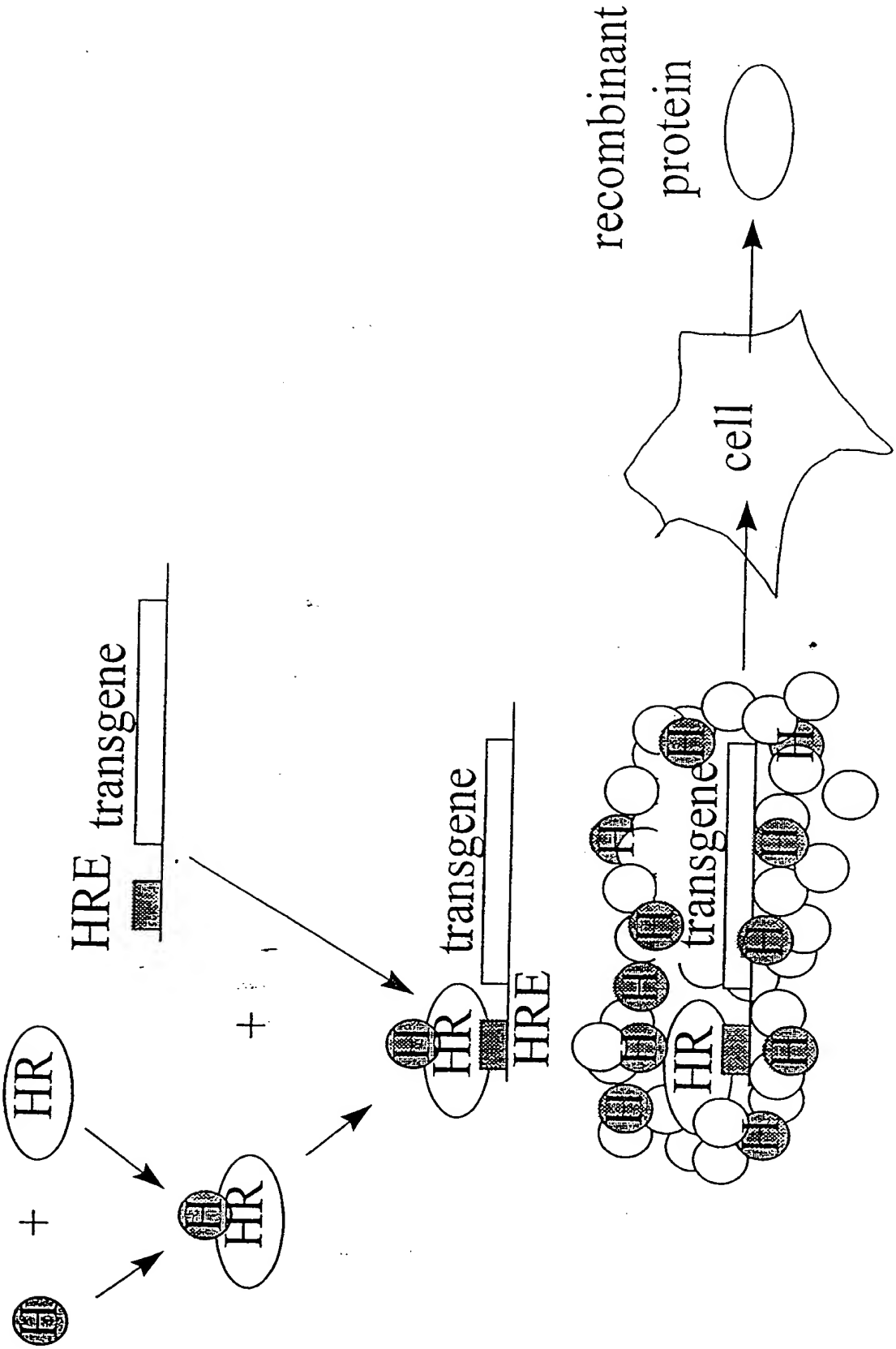
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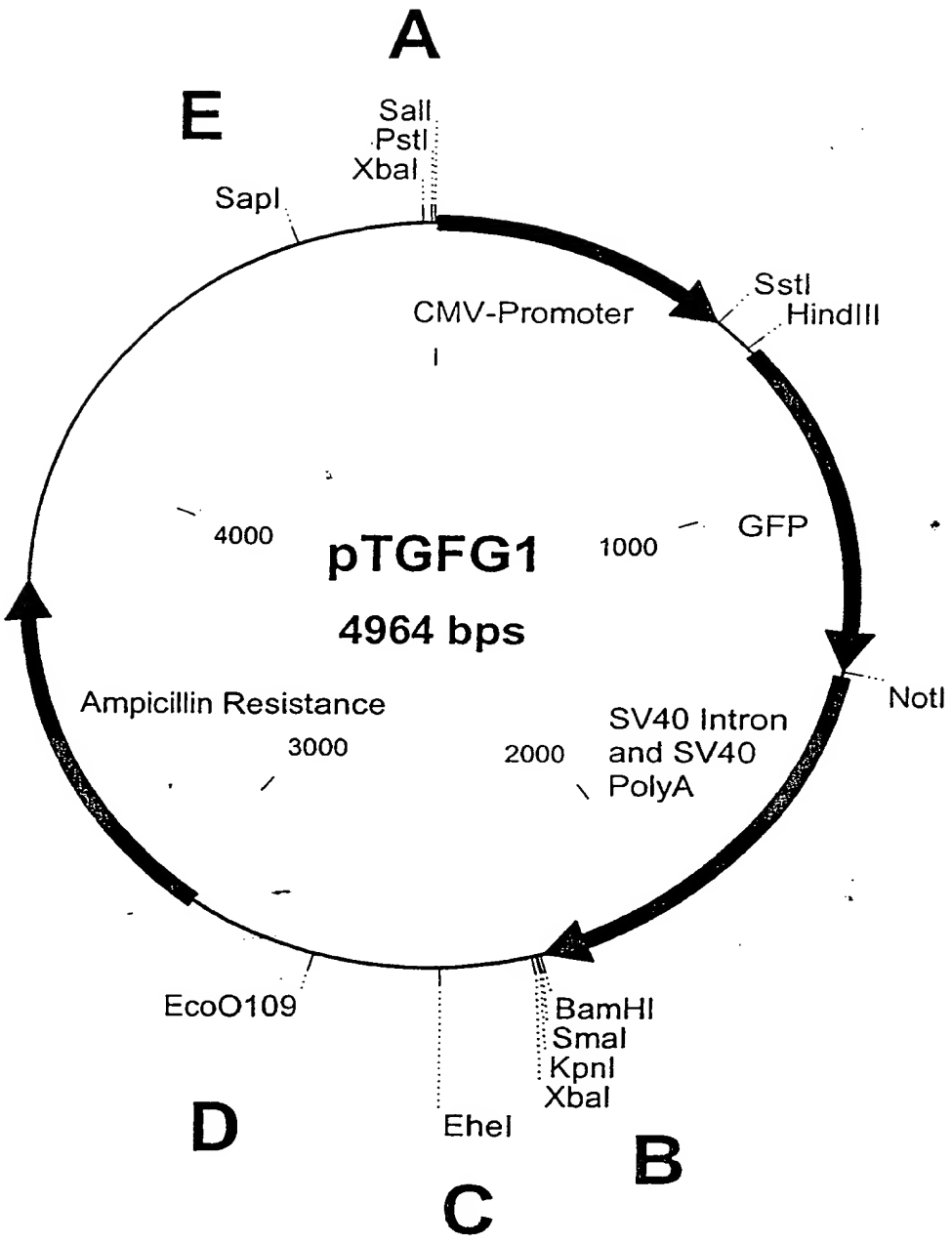
Fig. 2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NotI
Ampicillin Resistance
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EheI
D
B
C

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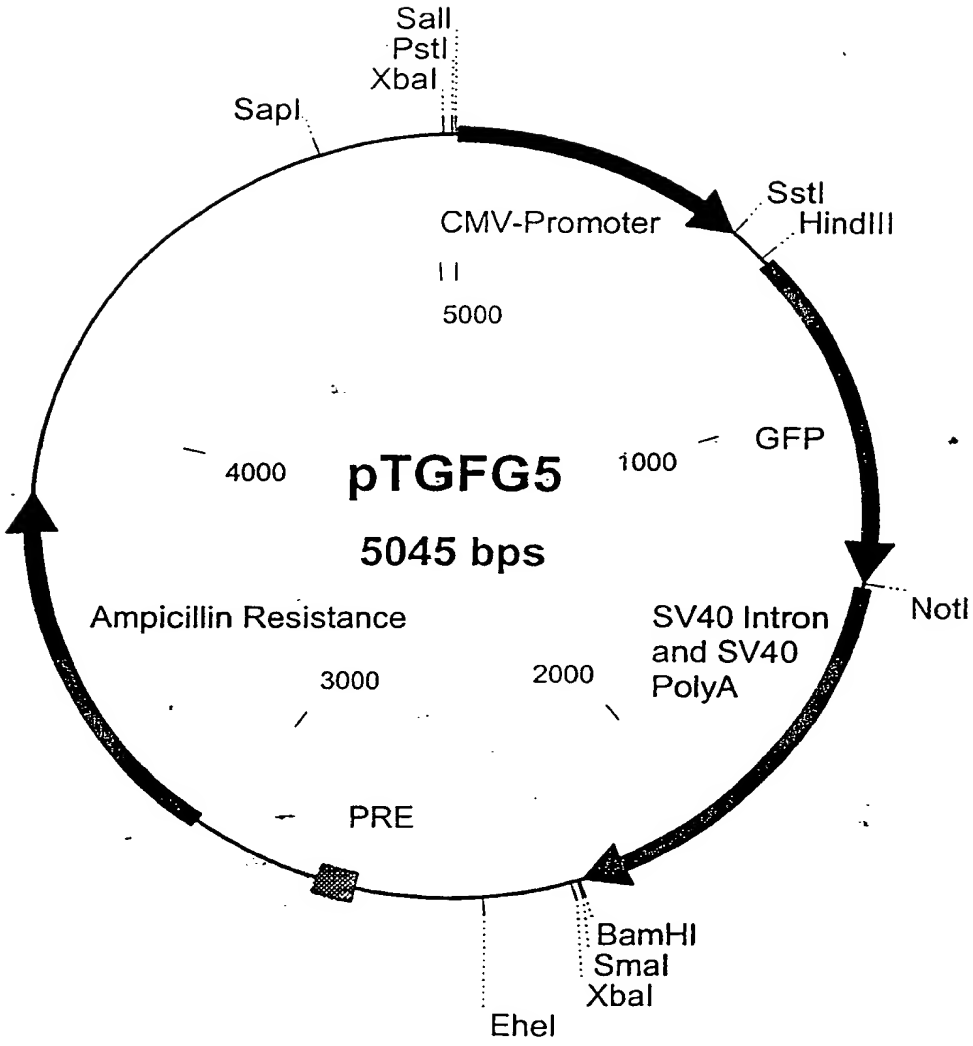
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Ampicillin Resistance
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and SV40
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2000
PRE
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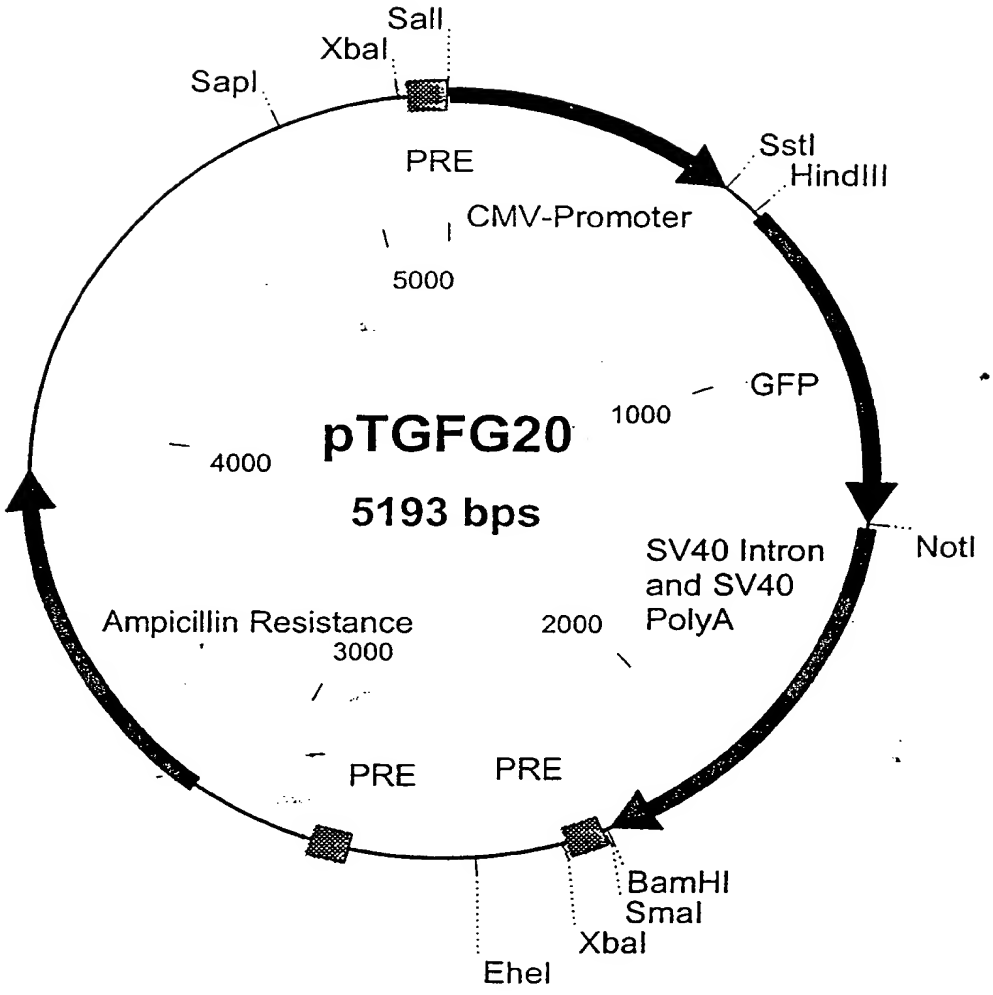
XbaI
EheI

Fig. 4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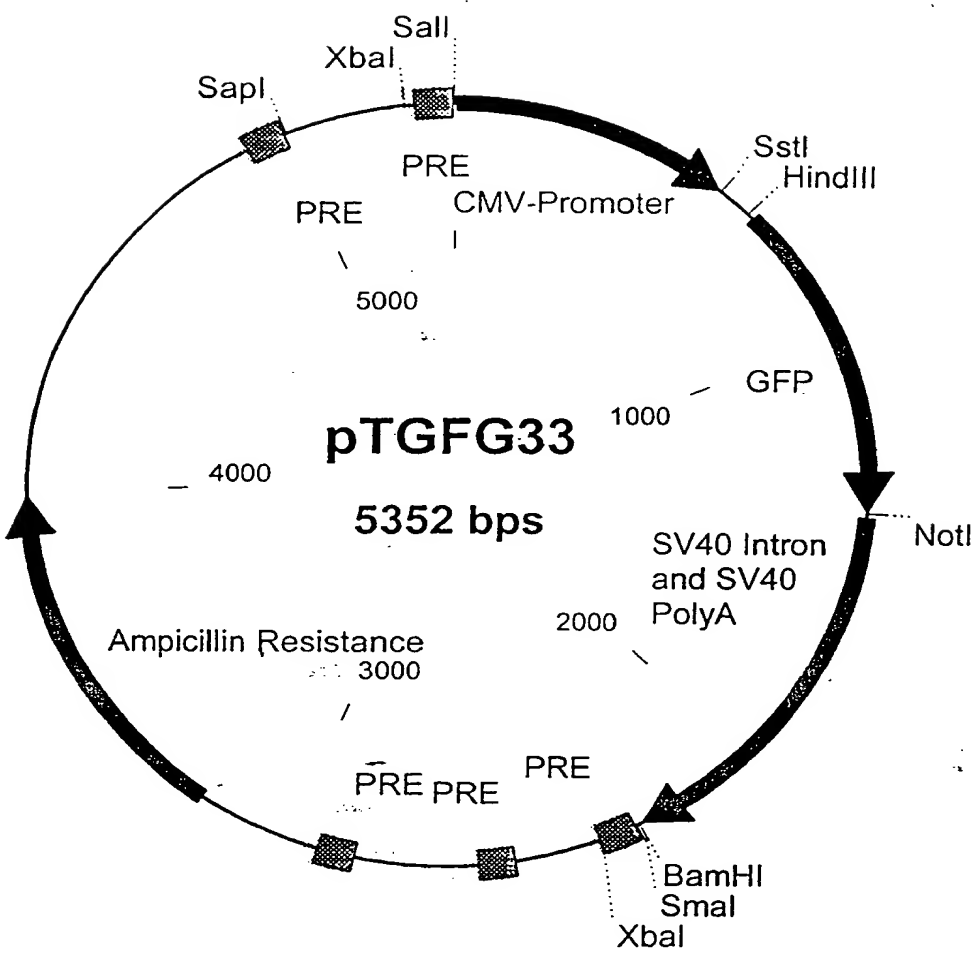
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Ampicillin Resistance
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PRE
PRE
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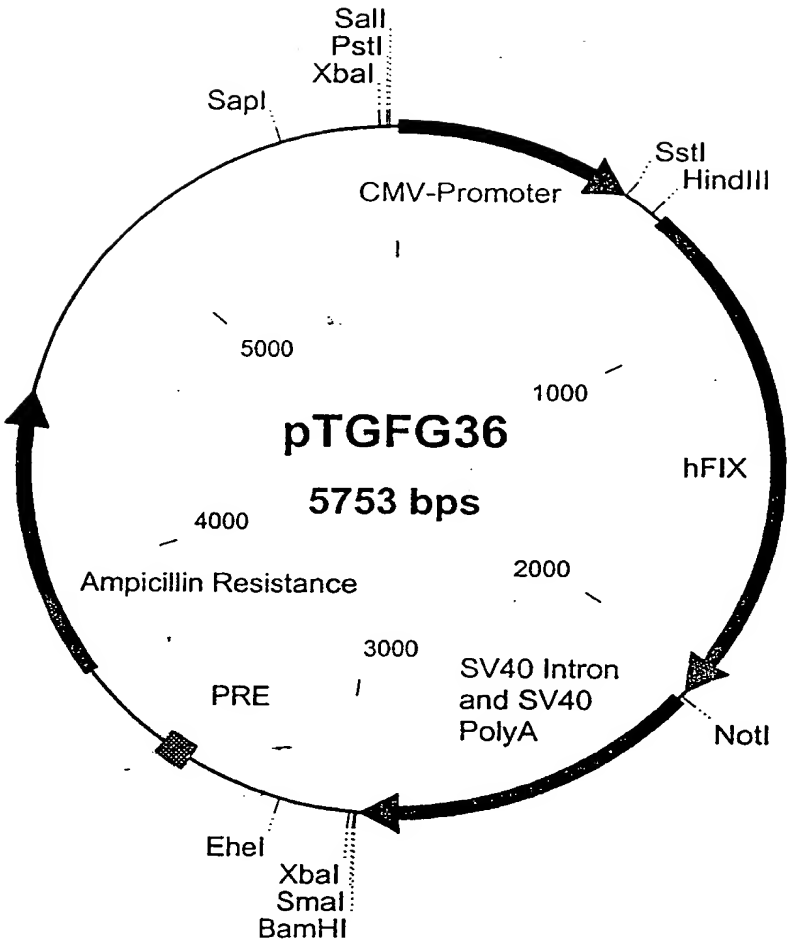
SmaI
XbaI

Fig. 6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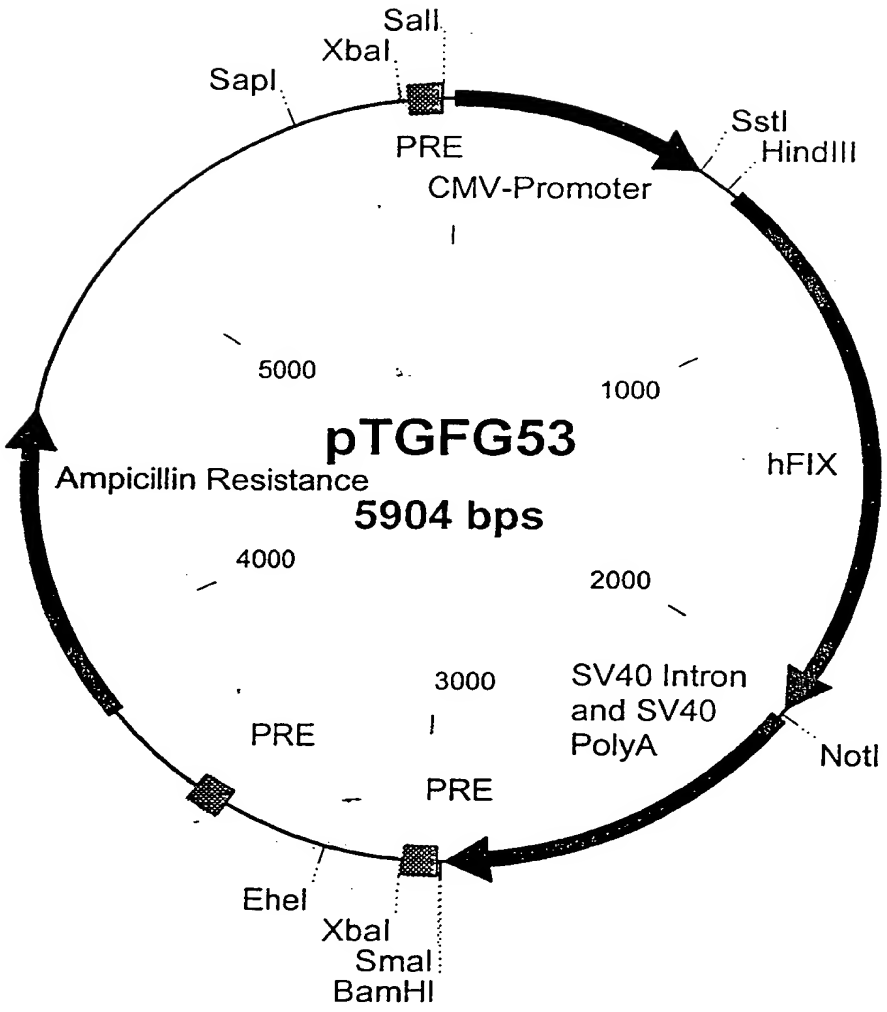
BamHI

Fig. 7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SmaI
BamHI
4000
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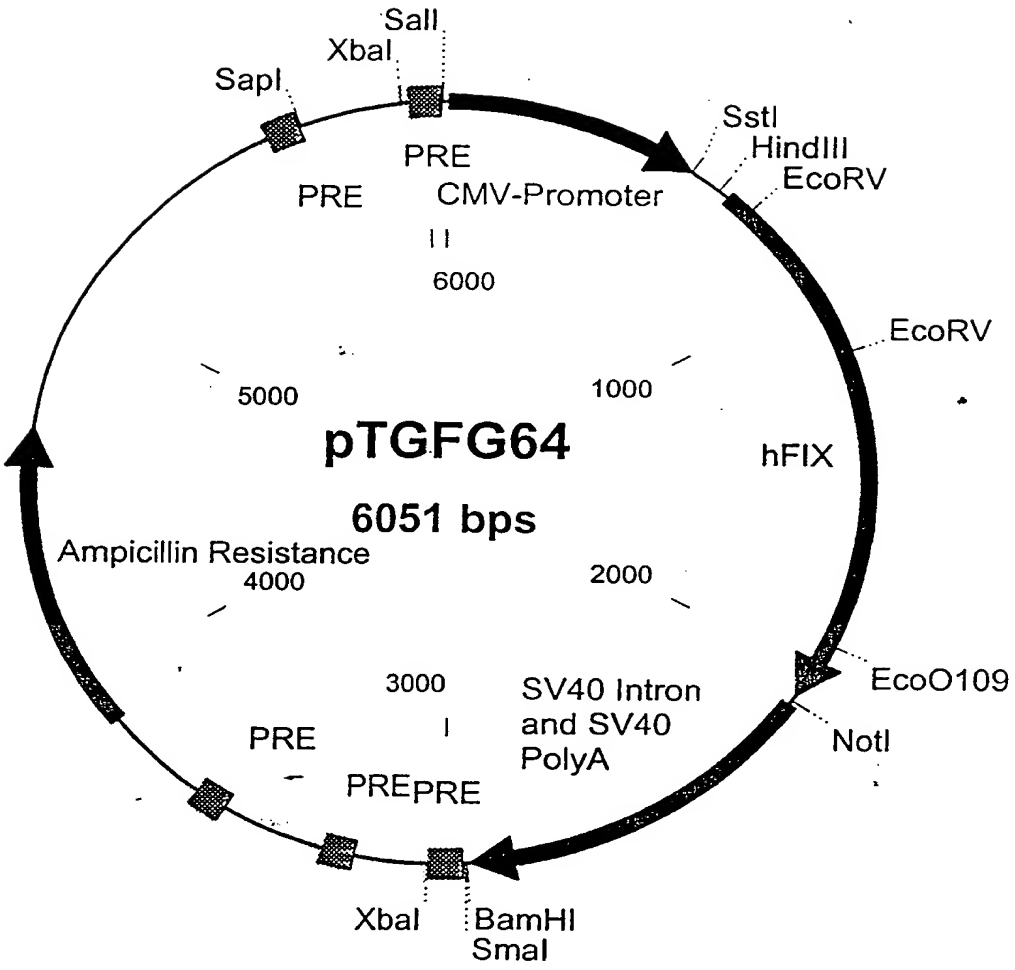
pTGFG53
5904 bps

Fig. 8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6051 bps
Ampicillin Resistance
4000
2000
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SV40 Intron
and SV40
PolyA
NotI
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PREPRE
XbaI
BamHI
SmaI

Fig. 9

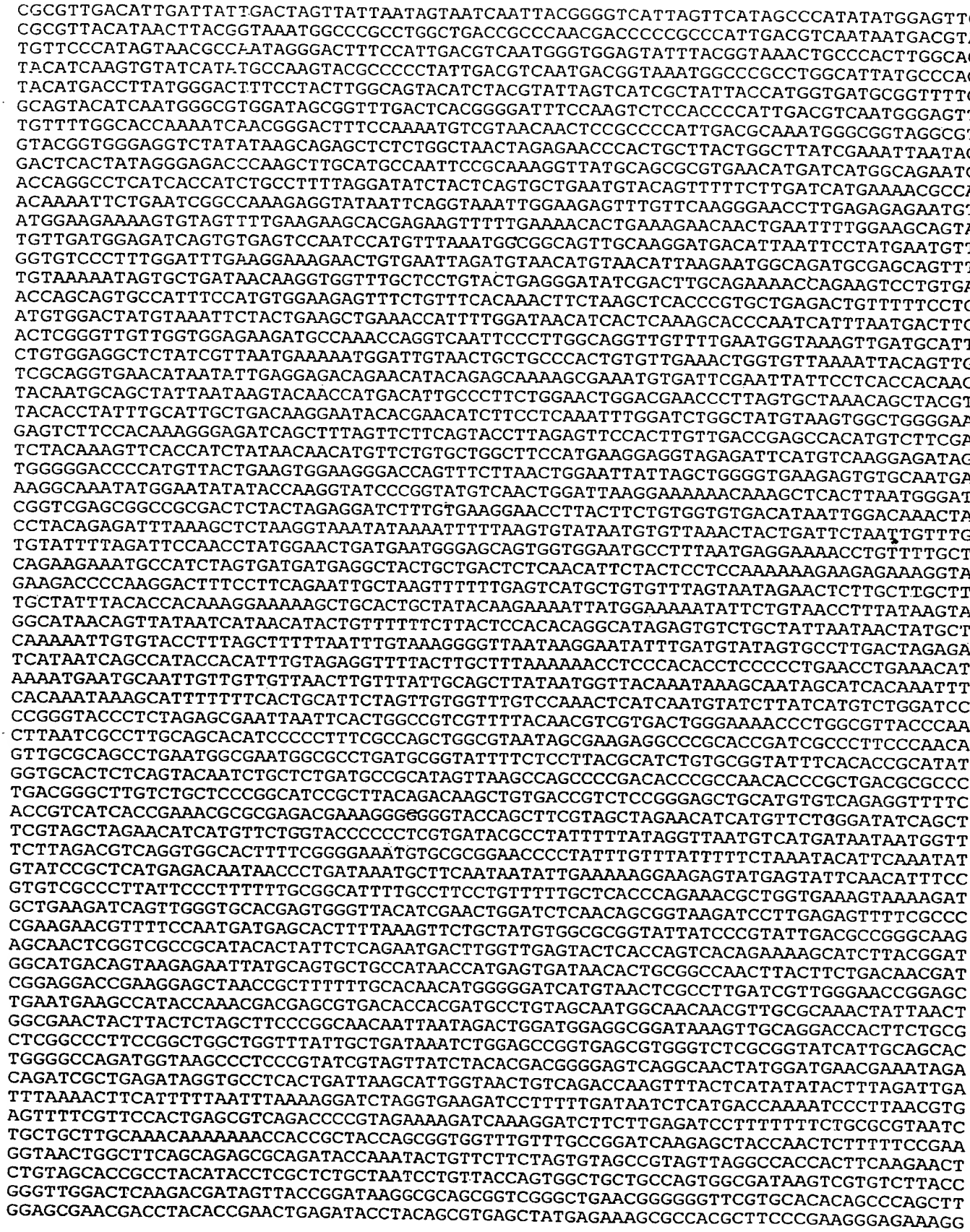
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Fig. 9 (continued)

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Fig. 10

```
Met Gln Arg Val Asn Met Ile Met Ala Glu Ser Pro Gly Leu Ile Thr
 1               5                  10                  15

Ile Cys Leu Leu Gly Tyr Leu Leu Ser Ala Glu Cys Thr Val Phe Leu
            20                  25                  30

Asp His Glu Asn Ala Asn Lys Ile Leu Asn Arg Pro Lys Arg Tyr Asn
        35                  40                  45

Ser Gly Lys Leu Glu Glu Phe Val Gln Gly Asn Leu Glu Arg Glu Cys
    50                  55                  60

Met Glu Glu Lys Cys Ser Phe Glu Glu Ala Arg Glu Val Phe Glu Asn
65                  70                  75                  80

Thr Glu Arg Thr Thr Glu Phe Trp Lys Gln Tyr Val Asp Gly Asp Gln
                85                  90                  95

Cys Glu Ser Asn Pro Cys Leu Asn Gly Gly Ser Cys Lys Asp Asp Ile
            100                 105                 110

Asn Ser Tyr Glu Cys Trp Cys Pro Phe Gly Phe Glu Gly Lys Asn Cys
        115                 120                 125

Glu Leu Asp Val Thr Cys Asn Ile Lys Asn Gly Arg Cys Glu Gln Phe
    130                 135                 140

Cys Lys Asn Ser Ala Asp Asn Lys Val Val Cys Ser Cys Thr Glu Gly
145                 150                 155                 160

Tyr Arg Leu Ala Glu Asn Gln Lys Ser Cys Glu Pro Ala Val Pro Phe
                165                 170                 175

Pro Cys Gly Arg Val Ser Val Ser Gln Thr Ser Lys Leu Thr Arg Ala
            180                 185                 190

Glu Thr Val Phe Pro Asp Val Asp Tyr Val Asn Ser Thr Glu Ala Glu
        195                 200                 205

Thr Ile Leu Asp Asn Ile Thr Gln Ser Thr Gln Ser Phe Asn Asp Phe
    210                 215                 220

Thr Arg Val Val Gly Gly Glu Asp Ala Lys Pro Gly Gln Phe Pro Trp
225                 230                 235                 240

Gln Val Val Leu Asn Gly Lys Val Asp Ala Phe Cys Gly Gly Ser Ile
                245                 250                 255

Val Asn Glu Lys Trp Ile Val Thr Ala Ala His Cys Val Glu Thr Gly
            260                 265                 270

Val Lys Ile Thr Val Val Ala Gly Glu His Asn Ile Glu Glu Thr Glu
        275                 280                 285

His Thr Glu Gln Lys Arg Asn Val Ile Arg Ile Ile Pro His His Asn
    290                 295                 300
```

Fig. 10 (continued)

```
Tyr Asn Ala Ala Ile Asn Lys Tyr Asn His Asp Ile Ala Leu Leu Glu
305                 310                 315                 320

Leu Asp Glu Pro Leu Val Leu Asn Ser Tyr Val Thr Pro Ile Cys Ile
                325                 330                 335

Ala Asp Lys Glu Tyr Thr Asn Ile Phe Leu Lys Phe Gly Ser Gly Tyr
            340                 345                 350

Val Ser Gly Trp Gly Arg Val Phe His Lys Gly Arg Ser Ala Leu Val
        355                 360                 365

Leu Gln Tyr Leu Arg Val Pro Leu Val Asp Arg Ala Thr Cys Leu Arg
    370                 375                 380

Ser Thr Lys Phe Thr Ile Tyr Asn Asn Met Phe Cys Ala Gly Phe His
385                 390                 395                 400

Glu Gly Gly Arg Asp Ser Cys Gln Gly Asp Ser Gly Gly Pro His Val
                405                 410                 415

Thr Glu Val Glu Gly Thr Ser Phe Leu Thr Gly Ile Ile Ser Trp Gly
            420                 425                 430

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Arg Tyr Val Asn Trp Ile Lys Glu Lys Thr Lys Leu Thr
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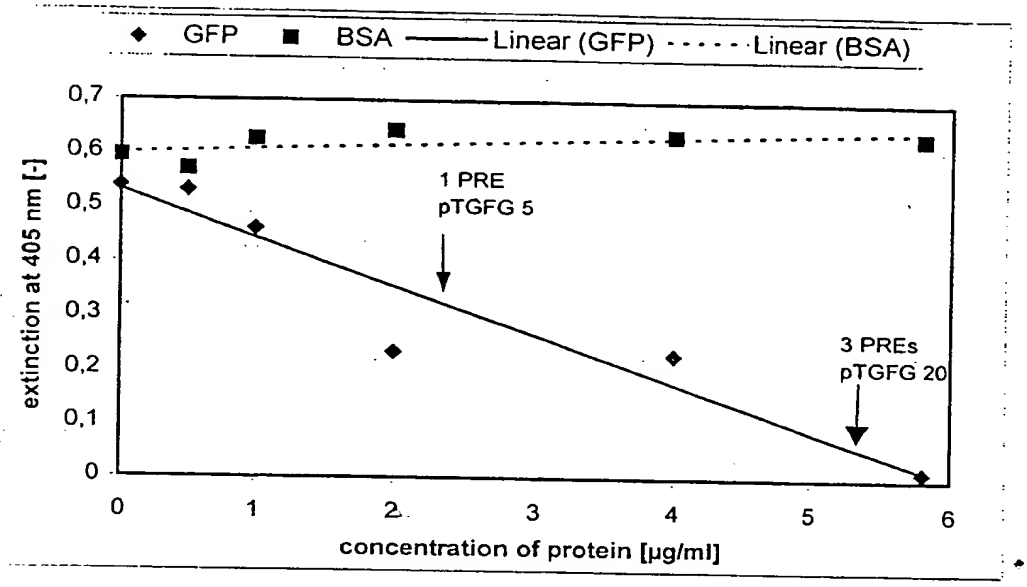
Fig. 11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3
4
5
6
concentration of protein [µg/ml]

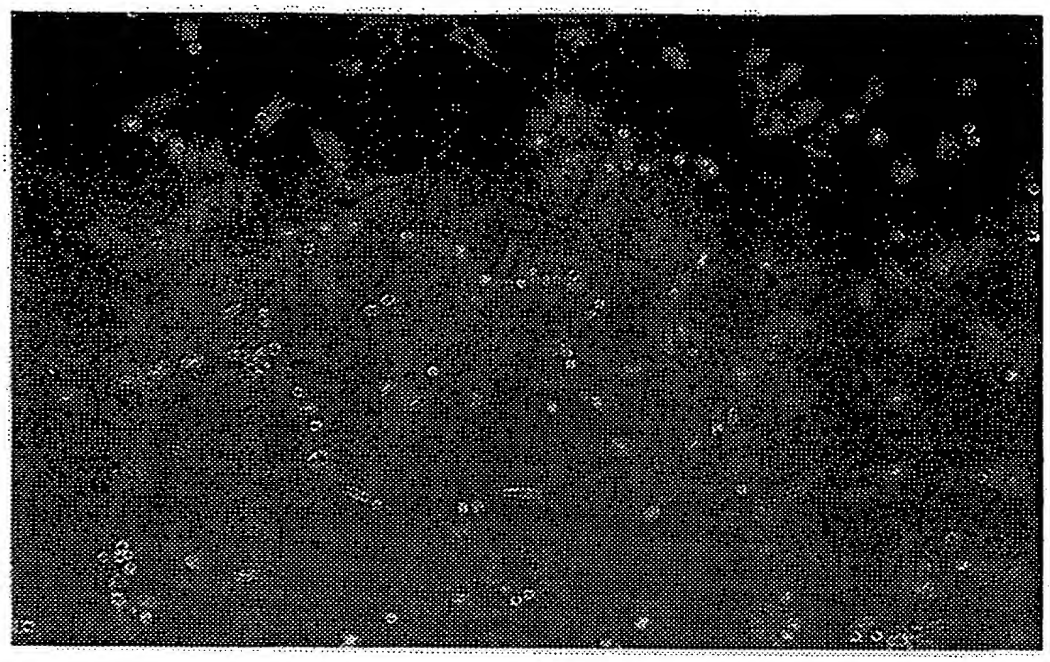


Fig. 12a

Fig 12 b

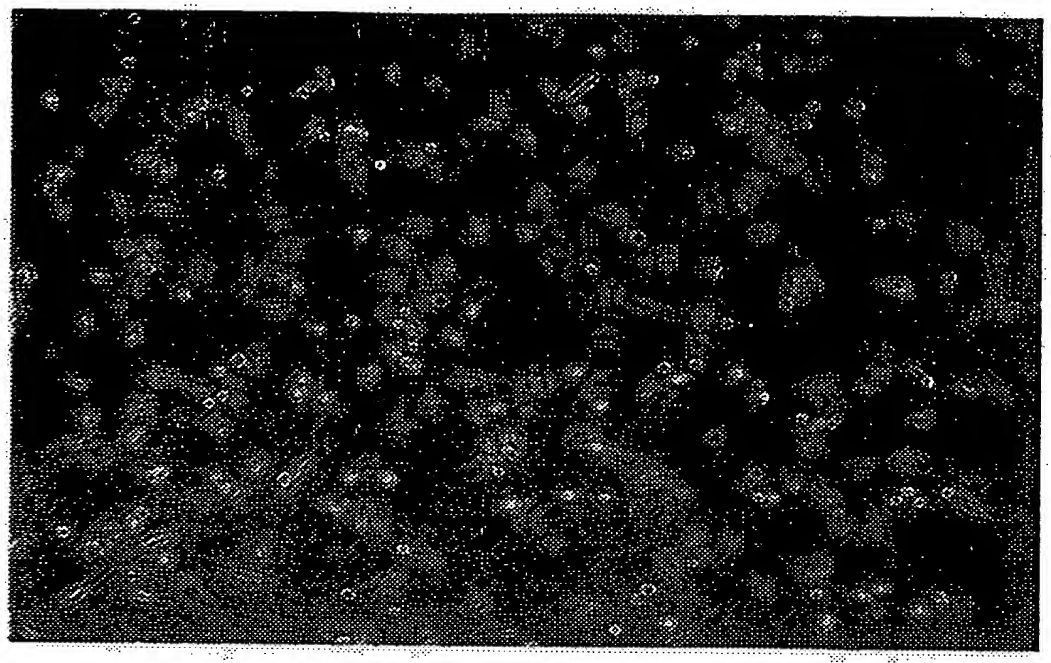


Fig 12 c

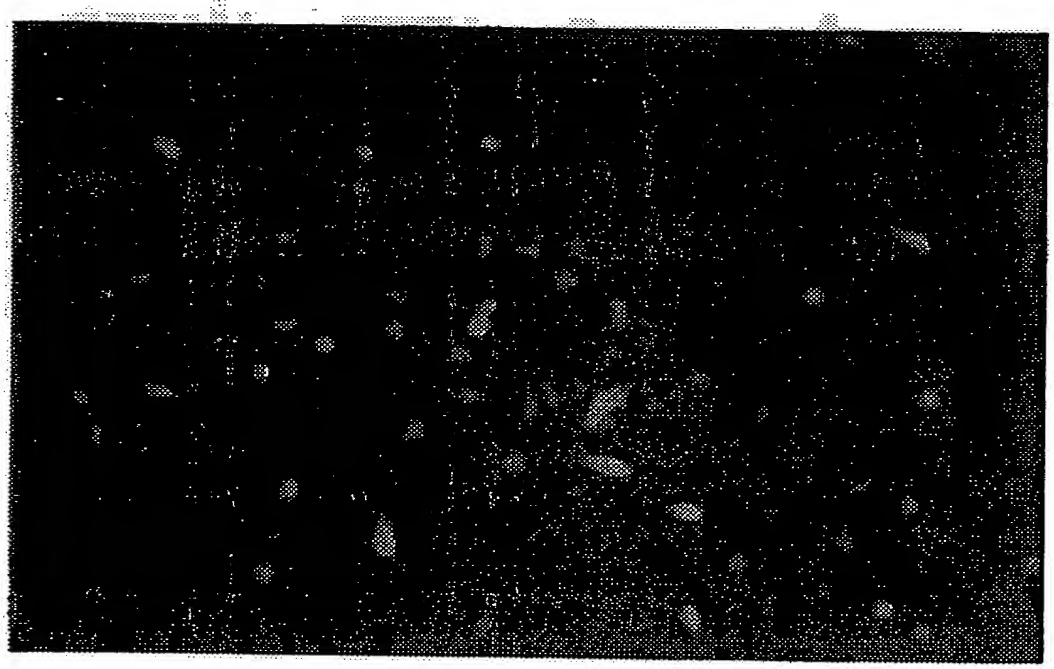


Fig 12 d

Fig. 13

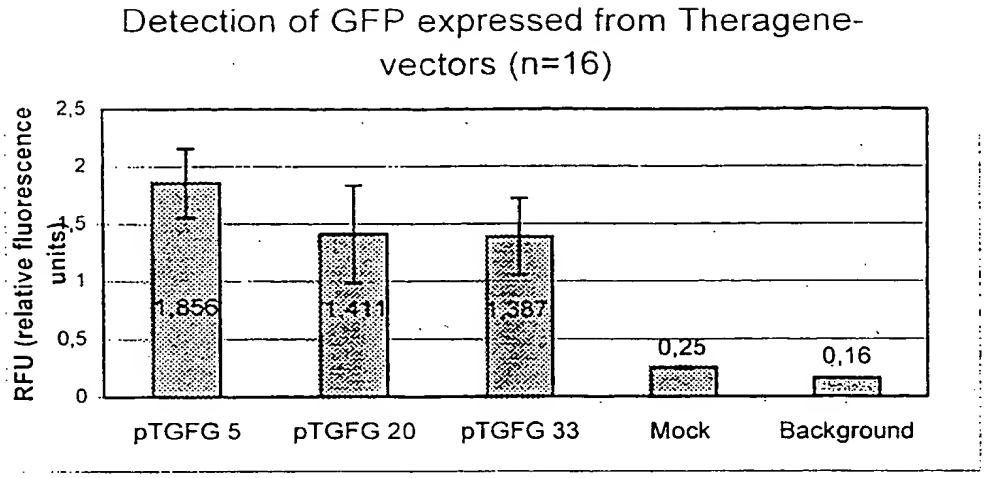


Fig. 14

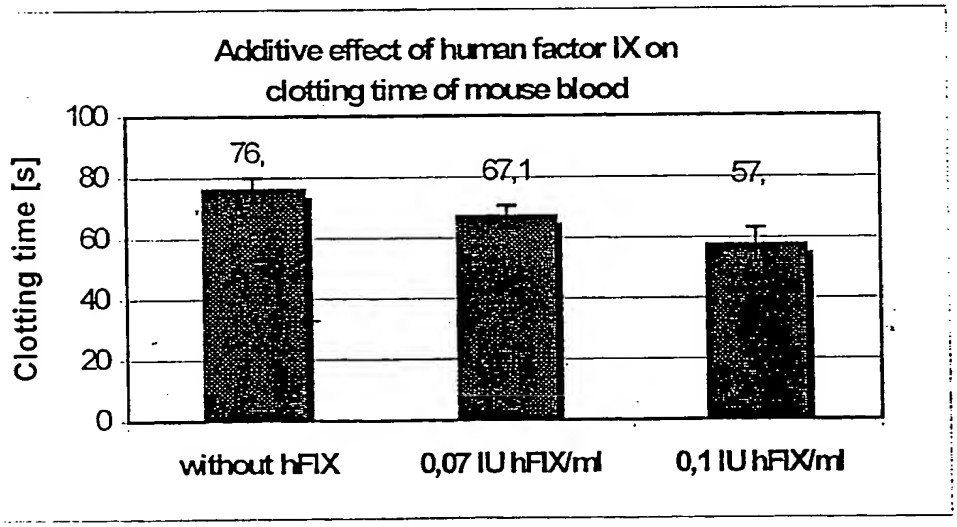
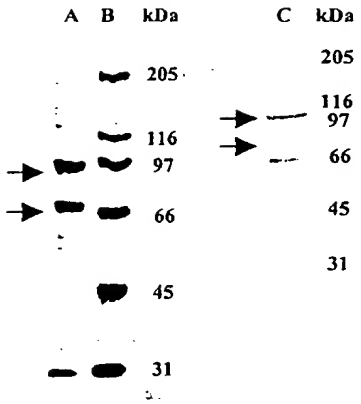


Fig. 15



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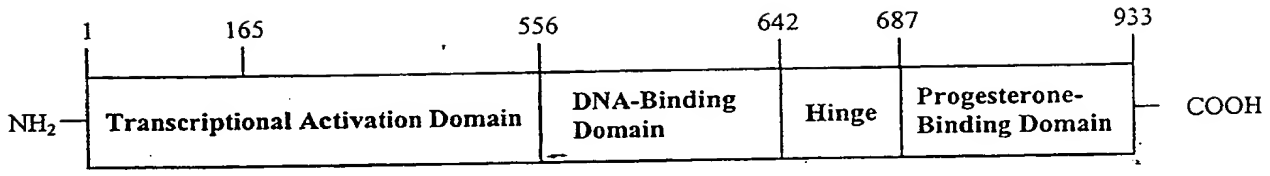
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DNA-Binding Domain
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Progesterone-Binding Domain
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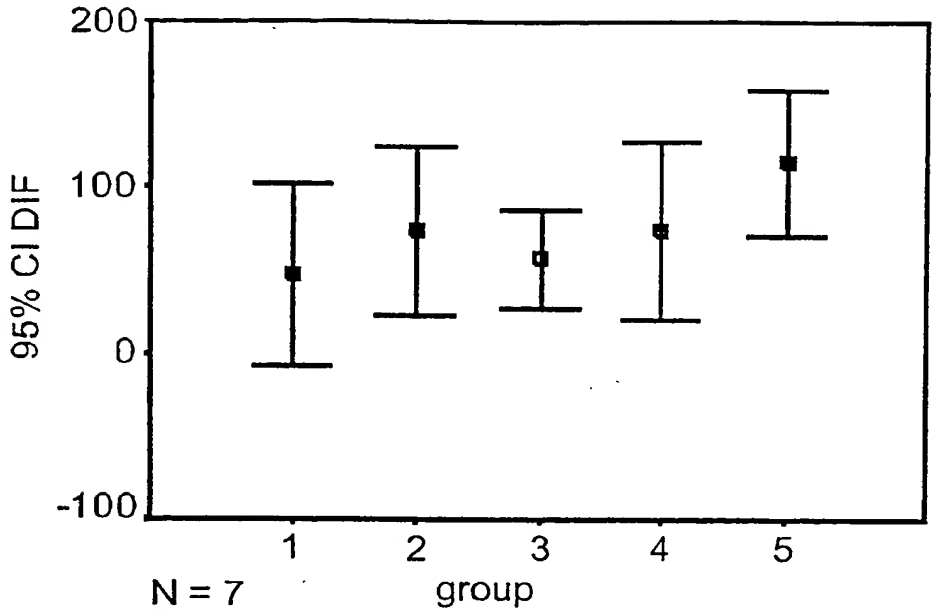
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Fig. 17

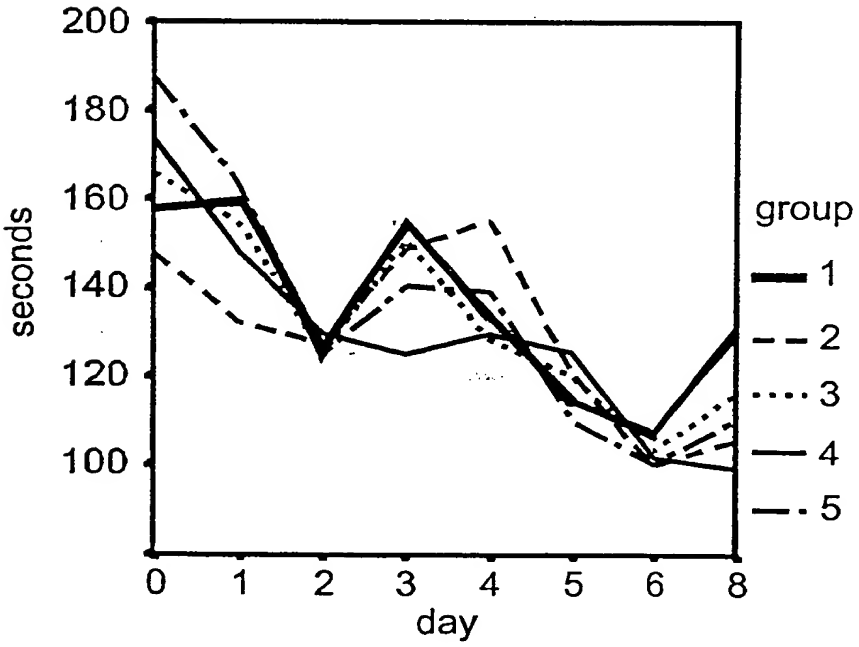
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Fig. 18

Fig. 19

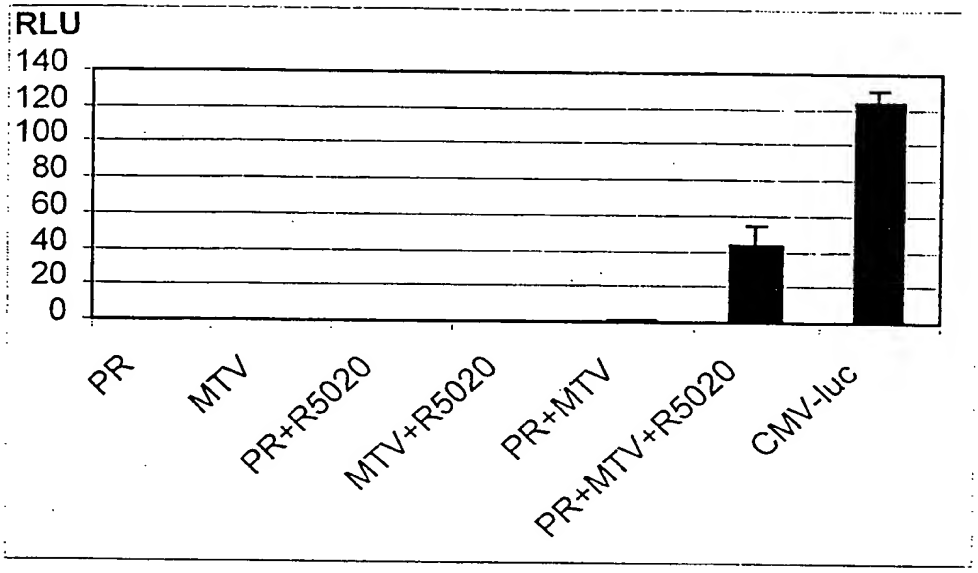
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Fig. 20

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Fig. 21

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aagcttgcat gccaattccg caaaggtt atg cag cgc gtg aac atg atc atg 712
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gca gaa tca cca ggc ctc atc acc atc tgc ctt tta gga tat cta ctc 760
Ala Glu Ser Pro Gly Leu Ile Thr Ile Cys Leu Leu Gly Tyr Leu Leu
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ctg aat cgg cca aag agg tat aat tca ggt aaa ttg gaa gag ttt gtt   856
Leu Asn Arg Pro Lys Arg Tyr Asn Ser Gly Lys Leu Glu Glu Phe Val
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caa ggg aac ctt gag aga gaa tgt atg gaa gaa aag tgt agt ttt gaa   904
Gln Gly Asn Leu Glu Arg Glu Cys Met Glu Glu Lys Cys Ser Phe Glu
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agc acc caa tca ttt aat gac ttc act cgg gtt gtt ggt gga gaa gat  1384
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<213> Artificial Sequence
<223> Description of Artificial Sequence: vector pTGFG36

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20 25 30

Asp His Glu Asn Ala Asn Lys Ile Leu Asn Arg Pro Lys Arg Tyr Asn
35 40 45

Ser Gly Lys Leu Glu Glu Phe Val Gln Gly Asn Leu Glu Arg Glu Cys
50 55 60

Met Glu Glu Lys Cys Ser Phe Glu Glu Ala Arg Glu Val Phe Glu Asn
65 70 75 80

Thr Glu Arg Thr Thr Glu Phe Trp Lys Gln Tyr Val Asp Gly Asp Gln
85 90 95

Cys Glu Ser Asn Pro Cys Leu Asn Gly Gly Ser Cys Lys Asp Asp Ile
100 105 110

Asn Ser Tyr Glu Cys Trp Cys Pro Phe Gly Phe Glu Gly Lys Asn Cys
115 120 125

Glu Leu Asp Val Thr Cys Asn Ile Lys Asn Gly Arg Cys Glu Gln Phe
130 135 140

Cys Lys Asn Ser Ala Asp Asn Lys Val Val Cys Ser Cys Thr Glu Gly
145 150 155 160

Tyr Arg Leu Ala Glu Asn Gln Lys Ser Cys Glu Pro Ala Val Pro Phe
165 170 175

Pro Cys Gly Arg Val Ser Val Ser Gln Thr Ser Lys Leu Thr Arg Ala
180 185 190

Glu Thr Val Phe Pro Asp Val Asp Tyr Val Asn Ser Thr Glu Ala Glu
195 200 205

Thr Ile Leu Asp Asn Ile Thr Gln Ser Thr Gln Ser Phe Asn Asp Phe
210 215 220

Thr Arg Val Val Gly Gly Glu Asp Ala Lys Pro Gly Gln Phe Pro Trp
225 230 235 240

Gln Val Val Leu Asn Gly Lys Val Asp Ala Phe Cys Gly Gly Ser Ile
245 250 255

Val Asn Glu Lys Trp Ile Val Thr Ala Ala His Cys Val Glu Thr Gly
260 265 270

Val Lys Ile Thr Val Val Ala Gly Glu His Asn Ile Glu Glu Thr Glu
275 280 285

His Thr Glu Gln Lys Arg Asn Val Ile Arg Ile Ile Pro His His Asn
290 295 300

Tyr Asn Ala Ala Ile Asn Lys Tyr Asn His Asp Ile Ala Leu Leu Glu
305 310 315 320

Leu Asp Glu Pro Leu Val Leu Asn Ser Tyr Val Thr Pro Ile Cys Ile
325 330 335

Ala Asp Lys Glu Tyr Thr Asn Ile Phe Leu Lys Phe Gly Ser Gly Tyr
340 345 350

Val Ser Gly Trp Gly Arg Val Phe His Lys Gly Arg Ser Ala Leu Val
355 360 365

Leu Gln Tyr Leu Arg Val Pro Leu Val Asp Arg Ala Thr Cys Leu Arg
370 375 380

Ser Thr Lys Phe Thr Ile Tyr Asn Asn Met Phe Cys Ala Gly Phe His
385 390 395 400

Glu Gly Gly Arg Asp Ser Cys Gln Gly Asp Ser Gly Gly Pro His Val
405 410 415

Thr Glu Val Glu Gly Thr Ser Phe Leu Thr Gly Ile Ile Ser Trp Gly
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Arg Tyr Val Asn Trp Ile Lys Glu Lys Thr Lys Leu Thr
450 455 460

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<211> 78
<212> DNA
<213> Homo sapiens

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atcatgttct ggtacccc 78

<210> 4
<211> 78
<212> DNA
<213> Homo sapiens

<400> 4
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ctacgaagct ggtacccc 78

<210> 5
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<212> DNA
<213> Homo sapiens

<400> 5
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<210> 6
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<400> 6
ggccgcttgc tcgaggtca 19

<210> 7
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<210> 8
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<210> 9
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<210> 10
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<210> 11
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<400> 11
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<210> 12
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<400> 12
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<210> 13
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<220>
<223> Description of Artificial Sequence: vector pTGFG53

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<212> DNA
<213> Artificial Sequence

<220>
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<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: vector pTGFG67

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<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: vector pTGFG82

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<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: vector pTGFG95

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INTERNATIONAL SEARCH REPORT

In. ational Application No
PCT/EP 00/01368

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C12N15/12 C12N15/57 C12N15/67 C12N15/85 C12N9/64
C07K14/72. C12Q1/68 A61K48/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C12N C07K C12Q A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and. where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X Y	WO 94 28150 A (UNIV MCGILL) 8 December 1994 (1994-12-08) page 5, line 1 - line 11 page 6, line 34 -page 7, line 10 page 6, line 24 - line 28 page 10, line 20 - line 25 page 14, line 14 - line 19 claims 1-11 --- -/--	1,2,6,7, 11,29,30 3-5,8,9

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure. use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents. such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
6 June 2000	26/06/2000

Name and mailing address of the ISA	Authorized officer
European Patent Office. P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040. Tx. 31 651 epo nl. Fax: (+31-70) 340-3016	Hornig, H

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INTERNATIONAL SEARCH REPORT

Int. ational Application No
PCT/EP 00/01368

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	V. BOONYARATANAKORNKIT ET AL.: "High-mobility group chromatin proteins 1 and 2 functionally interact with steroid hormone receptors to enhance their DNA binding in vitro and transcriptional activity in mamalian cells" MOL. CELL. BIOL., vol. 18, no. 8, August 1998 (1998-08), pages 4471-4487, XP002139580 ASM WASHINGTON, DC,US cited in the application the whole document	1,2,7
X	WO 94 17182 A (RES INST OF THE PALO ALTO MEDI ;LEAVITT JOHN C (US)) 4 August 1994 (1994-08-04) page 16, line 30 - line 36 page 17, line 1 - line 3; claims 1-16	1,2,6,7, 11,29,30
X	WO 93 20218 A (CONNAUGHT LAB ;FILMUS JORGE (CA); KLEIN MICHEL (CA)) 14 October 1993 (1993-10-14) the whole document	1,2,6,11
Y	WO 94 29471 A (GENETIC THERAPY INC) 22 December 1994 (1994-12-22) the whole document	3-5,8,9
A	WO 93 23431 A (BAYLOR COLLEGE MEDICINE) 25 November 1993 (1993-11-25) cited in the application the whole document	
A	BEATO M ET AL: "Transcriptional regulation by steroid hormones" STEROIDS: STRUCTURE, FUNCTION, AND REGULATION,US,ELSEVIER SCIENCE PUBLISHERS, NEW YORK, NY, vol. 61, no. 4, 1 April 1996 (1996-04-01), pages 240-251, XP004026583 ISSN: 0039-128X the whole document	
A	BEATO M: "GENE REGULATION BY STEROID HORMONES" CELL,US,CELL PRESS, CAMBRIDGE, NA, vol. 56, no. 3, 10 February 1989 (1989-02-10), pages 335-344, XP000051659 ISSN: 0092-8674 the whole document	

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INTERNATIONAL SEARCH REPORT

In. ational Application No
PCT/EP 00/01368

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	KURACHI S. ET AL: "Regulatory mechanism of human factor IX gene: Protein binding at the Leyden-specific region." BIOCHEMISTRY, (1994) 33/6 (1580-1591). , XP002139581 the whole document	
A	CROSSLEY M. ET AL: "Recovery from hemophilia B Leyden: An androgen-responsive element in the factor IX promoter." SCIENCE, (1992) 257/5068 (377-379). , XP002139582 the whole document	

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INTERNATIONAL SEARCH REPORT

Information on patent family members

Int .tional Application No
PCT/EP 00/01368

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9428150 A	08-12-1994	US 5512483 A	30-04-1996
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